Pharmacoeconomic Profile of Paclitaxel as a First-Line Treatment for Patients with Advanced Ovarian Carcinoma

A Lifetime Cost-Effectiveness Analysis

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BACKGROUND. Analysis of published survival curves has recently been proposed as a method for conducting incremental cost-effectiveness analysis in which two treatments are compared with each other in terms of cost per year of life gained. In patients with advanced ovarian carcinoma, the combination of paclitaxel and cisplatin has been reported to improve survival more significantly than standard therapy with cyclophosphamide and cisplatin. However, the high cost of paclitaxel indicates a need for an evaluation of the pharmacoeconomic profile of these treatments.

METHODS. The authors conducted an incremental cost-effectiveness analysis to assess the paclitaxel-based regimen in terms of cost per year of life gained. The analysis utilized data from a published controlled long term trial involving 184 patients treated with paclitaxel and cisplatin and 202 patients treated with cyclophosphamide and cisplatin. Gompertz' law was employed to obtain the lifetime estimate of the years gained by patients given the first treatment in comparison with patients given the second.

RESULTS. The paclitaxel-based treatment was found to improve life expectancy by 46 years for every 100 patients. Costs of chemotherapy were higher in the paclitaxel group than in the standard-therapy group (the cost difference was $901,723 for every 100 patients; costs for treating febrile neutropenia induced by chemotherapy were taken into account). On the basis of these data of cost and effectiveness, the administration of paclitaxel and cisplatin was found to imply a cost per year of life gained of $19,603 more than standard chemotherapy.

CONCLUSIONS. The pharmacoeconomic profile of paclitaxel compares favorably with economic data previously calculated for other types of pharmacologic treatment. *Cancer* **1996; 78:2366–73.** © *1996 American Cancer Society.*

KEYWORDS: paclitaxel, pharmacoeconomics, cost-effectiveness, ovarian carcinoma.

In patients with advanced ovarian carcinoma, the administration of paclitaxel and cisplatin as a first-line treatment has been reported to improve survival as compared with subjects given a standard regimen based on cyclophosphamide and cisplatin.[1–4] In this study, we assessed the pharmacoeconomic profile of these two chemotherapeutic modalities by determining the cost per year of life gained relative to the combination of paclitaxel and cisplatin in comparison with the combination of cyclophosphamide and cisplatin. Our pharmacoeconomic analysis employed the lifetime approach, according to which both costs and benefits are projected for the long term to cover the whole life span of all patients. Recent trends in the area of pharmacoeconomic studies[5–9] recommend this new methodology of data analysis.

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MATERIALS AND METHODS

Clinical Data Included in the Analysis

We used the clinical data of a published controlled trial[1] involving 184 patients with advanced ovarian carcinoma treated intravenously with paclitaxel (135 mg per m^2 of body-surface area) plus cisplatin (75 mg per m^2 of body-surface area) and 202 patients treated intravenously with cyclophosphamide (750 mg per m^2 of body-surface area) plus cisplatin (75 mg per m^2 of body-surface area). Both regimens were given every 3 weeks, for a total of 6 courses. The women assigned to the paclitaxel group were premedicated intravenously with dexamethasone (20 mg), diphenhydramine (50 mg), and ranitidine (50 mg). Both groups received an average of 5.6 cycles. The last time point in the graph of the survival curves was 4 years.

Cost-Effectiveness Analysis Based on Survival Data

In pharmacoeconomic analysis, the particular costs and benefits vary with the perspective of the study, and the analysis can in fact be constructed to reflect the viewpoint of society as a whole, payers, health care providers, or patients. In this study, costs were assessed from a social perspective and were considered to reflect only the expenses of health care resources, i.e., direct costs, not indirect expenses such as wages or productivity lost because of illness or death. Our cost-effectiveness analysis proceeded through the following phases:

1. Estimates were obtained of the direct costs of treating 100 patients with either paclitaxel and cisplatin or cyclophosphamide and cisplatin (including costs of administration, nursing time, equipment used, etc.). Because the trial of McGuire et al.[1] found an increased incidence of febrile neutropenia in the paclitaxel group, an estimate was obtained of the incremental cost caused by this increased frequency, which was then added to the overall costs. Finally, the incremental cost of the paclitaxel-based regimen (as compared with the standard treatment) was calculated from the difference between the costs of the two patient groups.
2. The published survival curve of patients receiving the paclitaxel-based regimen was analyzed. In particular, the actuarial percentages of survival at various time points of the follow-up were determined from the published graph. These survival percentages were used to calculate the total area under the survival curve (AUC) from zero time to infinity with a weighted least-squares procedure of survival curve fitting. This total area (Fig. 1) was estimated as the sum of the area directly measured within the trial (i.e., the area from zero time to the last time point of the follow-up) plus the extrapolated right tail (i.e., the area from the last point of the follow-up to infinity). $AUC_{0->infinity}$, which denotes the area from time zero to infinity, is therefore the sum of $AUC_{0->last\ time\ point}$ and $AUC_{last\ time\ point->infinity}$. Both these components of the total area were determined according to Gompertz' law,[5,7-8,10-12] using the parameters generated by our survival curve fitting. The value of total AUC in the paclitaxel group is denoted as AUC_{PC}.
3. The survival curve of the group given cyclophosphamide and cisplatin was analyzed by the same procedure described for the data of patients given paclitaxel and cisplatin. In this case, the estimation yielded the value denoted AUC_{CC}.
4. The incremental clinical benefit derived from the paclitaxel regimen was calculated as AUC_{PC} minus AUC_{CC} (corrected for the different size of the two patient groups and normalized to a population of 100 patients). This difference is an estimate of the number of years of life gained for every 100 patients given paclitaxel and cisplatin rather than cyclophosphamide and cisplatin.
5. The incremental cost-effectiveness ratio (expressed on the basis of the cost per year of life gained) was calculated by dividing the incremental cost by the incremental benefit.

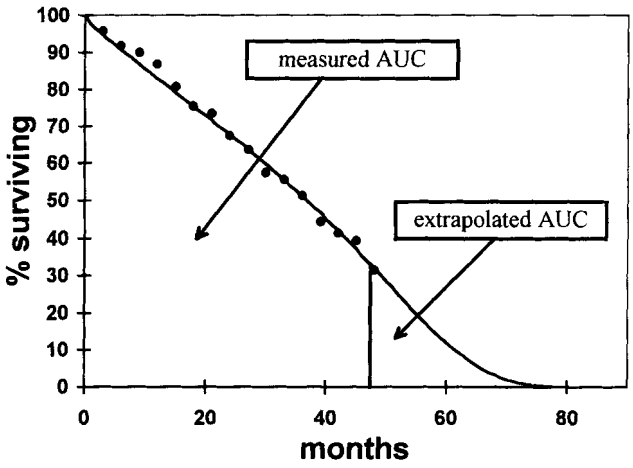

FIGURE 1. Measured area under the survival curve (AUC) and extrapolated AUC in the survival curve fitting are represented. Measured AUC corresponds to the time interval from zero to the last time point in the survival curve, whereas extrapolated AUC corresponds to the so-called "right tail" relative to the time interval from the last time point of the survival curve to infinity.

Survival Curve Fitting and Area Estimations

Gompertz' law[5,7-8,10-12] was used to describe the time course of a survival curve. Its equation is as follows:

$$SP = f(t) = 100\, s^{g^{t}} \quad c$$

where SP is the survival percentage in the survival curve; t is time; and s, g, and c are the three constants.

In our curve-fitting procedures, the numerical values of the SP-versus-t data pairs of the survival curve were estimated from the published graph by careful measurement of the height of every step of the curve. Then a nonlinear weighted least-squares iterative fit was started to determine the best-fit values for the three model parameters (s, g, and c). When the iterative process achieved what is known as convergence, the value of the weighted sum of squared residuals (WSSR) between fitted and observed percentages produced by the final estimates of the parameters was calculated. An index of the goodness of fit was then determined by calculating the root mean squared error (RMSE),[13] which is the square root of WSSR/n (where n is the number of SP vs. time data pairs). Considering the statistical weight adopted (weight = 1/squared SP), the units of RMSE are essentially those of a percentage number. Estimations of areas under the survival curve were carried out by standard numerical integration.

All mathematical calculations were performed using a specific microcomputer program.[10] Our computerized procedure executed the least-squares analysis using the fitting procedures contained in a commercial microcomputer program (PCNONLIN Version 4.0, Scientific Consulting Inc., Apex, NC).

Sensitivity Analysis

To account for the variability of costs related to drug administration (including drug prices), in our first sensitivity analysis we introduced ±20% variations in these data. In our second sensitivity analysis, we tested the effect of ±20% variations on costs derived from hospitalization, day hospital, and in-hospital management of neutropenic fever. A third sensitivity analysis was carried out in which we exclusively used the AUC values from 0 to 4 years. The two extrapolated tails were therefore disregarded in this latter analysis. The cost-effectiveness ratio was recalculated from the modified data of these three sensitivity analyses.

Discounting Clinical and Economic Data

In cost-effectiveness analyses, conventional practice[14] discounts either costs or both costs and benefits at an annual discount rate of 5%. Costs of the two different chemotherapeutic regimens were presumably incurred exclusively during the first year of the patients' follow-up. Because of the customary practice of discounting costs at yearly intervals, there was no need to discount costs because these were presumably not incurred after the first year of follow-up.

In the primary analysis of our study, benefits were not discounted, in accordance with the most recent trends emerging from the literature on this topic.[14] However, the effect of discounting benefits was assessed in a secondary analysis in which a standard 5% annual discount rate was introduced.

RESULTS

Estimation of Direct Costs

Direct costs were estimated as the sum of costs from the following sources: a) drug administration (including drug cost), b) hospitalization or day hospital, and c) cases of febrile neutropenia. Table 1 summarizes the direct costs related to the administration of the two chemotherapeutic regimens (cost per 100 subjects: $986,002 for paclitaxel and cisplatin, including supportive therapy to prevent hypersensitivity reactions, vs. $252,279 for cyclophosphamide and cisplatin). Antiemetic agents were not included in our estimation of incremental costs because the two patient groups were assumed to receive the same treatment.

Because paclitaxel administration requires a 24-hour intravenous infusion, patients of this group were assumed to require 1 day of hospitalization (total cost per 100 patients = $196,000, assuming a cost of about $350 per day of hospitalization according to the data presented by Uyl-de Groot et al.[15] and Glaspy and Jackway[16] and an average of 5.6 days of hospitalization per patient). Patients of the cisplatin and cyclophosphamide group, to whom chemotherapy was given by 2-hour intravenous infusion on day-hospital basis, were assigned a cost of $84,000 per 100 patients (assuming a day hospital cost of about $150 per day, according to Uyl-de Groot et al. and Glaspy and Jackway, and an average of 5.6 days per patient).

The rates of febrile neutropenia reported by McGuire et al. were 15% for the paclitaxel group versus 8% for the control group (in this analysis, febrile neutropenia[17] was defined as Grade 4 neutropenia with Grade 2, 3, or 4 fever). The cost of treating an episode of infection was estimated to be around $8000, according to Glaspy and Jackway. Hence, the costs related to the treatment of neutropenic fever were estimated as $120,000 in the paclitaxel group and $64,000 in the standard-treatment group.

Considering the three sources of cost, the overall cost in the paclitaxel group was estimated as $986,002 + 196,000 + 120,000 = $1,302,002 per 100 subjects. The three corresponding figures in the cyclophosphamide group were $252,279 + 84,000 + 64,000, yielding

TABLE 1
Dosage and Costs of Chemotherapy with Cyclophosphamide and Cisplatin Compared with Paclitaxel and Cisplatin

Drug (iv)	Dose per administration	Dose per patient per day[a]	Total no. of days of administration per cycle	Drug cost per 100 mg[b]	Cost per cycle per patient[c]	Cost per 100 patients[d]
Cyclophosphamide group						
Cisplatin	75 mg/m^2	122.25 mg	1	$325.48	$397.89	$222,823.00
Cyclophosphamide	750 mg/m^2	1237.5 mg	1	$4.25	$52.60	$29,456.00
Total					$450.42	$252,279.00
Paclitaxel group						
Cisplatin	75 mg/m^2	122.25 mg	1	$325.48	$397.89	$222,823.00
Paclitaxel	135 mg/m^2	222.75 mg	1	$608.80	$1356.00	$759,360.00
Dexamethasone	20 mg	20 mg	1	$5.71	$1.14	$638.40
Ranitidine	50 mg	50 mg	1	$7.98	$3.99	$2234.00
Diphenhydramine	50 mg	50 mg	1	$3.37	$1.69	$946.40
Total					$1761.00	$986,002.00

iv: intravenous.
[a] Dosages were calculated for a woman with body weight of 60 kg and body surface of 1.65 m^2.
[b] All drug prices refer to the U.S. market (*Red Book*, 1995 edition).
[c] The cost per patient was calculated from the exact drug dosages, assuming no waste of unused products.
[d] It was assumed that all patients in both the paclitaxel group and the cyclophosphamide group received a total of 5.6 cycles of chemotherapy (average value reported by McGuire et al.[1]).

TABLE 2
Percentages of Survival in the Paclitaxel and Cisplatin Group and the Cyclophosphamide and Cisplatin Group

Paclitaxel Group		Cyclophosphamide group	
Time (mos)	Survival (%)	Time (mos)	Survival (%)
0	100	0	100
3	96	3	93.9
6	91.9	6	87.9
9	89.9	9	81.8
12	86.8	12	76.8
15	80.8	15	68.7
18	75.7	18	59.6
21	73.7	21	55.6
24	67.6	24	50.5
27	63.6	27	44.4
30	57.6	30	41.4
33	55.5	33	35.4
36	51.5	36	31.3
39	44.4	39	29.3
42	41.4	42	25.2
45	39.4	45	25.2
48	31.3	48	25.2

TABLE 3
Results of Survival Curve Fitting after Lifetime Analysis of the Data of the Two Patient Groups

Values	Paclitaxel and cisplatin group[a]	Cyclophosphamide and cisplatin group[a]
$AUC_{0->infinity}$ (mos)[b]	3544	2997
$AUC_{0->last\ time\ point}$ (mos)[b]	3217	2539

AUC: area under the survival curve; 0–>infinity: from time zero to infinity; 0–last time point: from time zero to last time point of follow-up.
[a] Best-fit Gompertz parameters: paclitaxel and cisplatin curve, s = 0.987255, g = 0.988089, c = 1.082079; cyclophosphamide and cisplatin curve, s = 0.971147, g = 0.997383, c = 1.071500. (Note: Six decimal digits are needed to characterize the parameters of Gompertz' law appropriately[7]).
[b] Values were normalized to a population of 100 subjects.

a total of $400,279 per 100 subjects. The difference in cost between the two patient groups was $901,723 per 100 subjects.

Survival Curve Fitting

In our analysis of the survival curves of the two patient groups, we first estimated the values of survival percentage over time from the published graphs of the study by McGuire et al.[1] (Table 2). Then we carried out the least-squares curve-fitting procedure, the results of which are summarized in Table 3.

The fit was excellent for both curves (as demonstrated by the RMSE values, which were both less than 1%). As shown in Figure 2, both extrapolated right tails (which are, by definition, estimated less precisely) gave a relatively small contribution to the total values of AUC (9.2% for the paclitaxel group and 15.3% for the cyclophosphamide group). The incremental effectiveness of paclitaxel versus standard therapy was estimated to be equal to 46 undiscounted years of life for every 100 patients.

To assess whether the extrapolations to infinity produced by our analysis were realistic, we compared the curves reported in Figure 2 with the age data of the patients included in the study by McGuire et al.

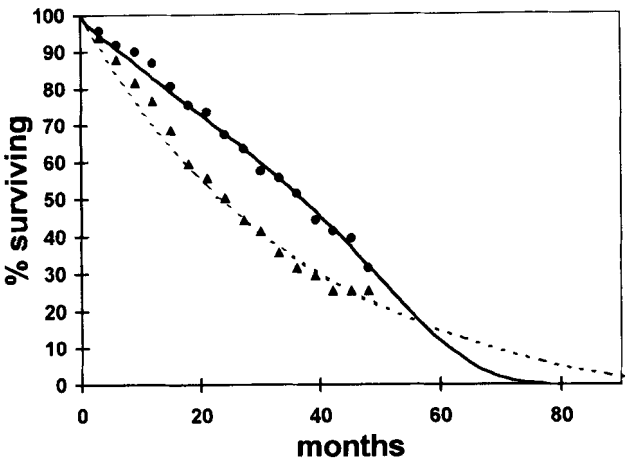

FIGURE 2. Survival curves for the paclitaxel and cisplatin group (circles) and the cyclophosphamide and cisplatin group (triangles), with extrapolation to infinity, are represented.

The median age at enrollment, i.e., at time zero in the graphs of Figure 2, was 60 years (range, 27–80) in the standard-therapy group versus 59 years (range, 20–84) in the paclitaxel group. If one, for example, considers the data of the paclitaxel group, our extrapolations demonstrate that the longest survival after the closing of the McGuire et al. study at 48 months was an additional 18 months (this value is the life expectancy after follow-up for the 5% of the paclitaxel group estimated directly from our extrapolated curve). This means that our extrapolations assume that a small subgroup of patients in the McGuire et al. study survived for a total of 4 + 1.5 years, i.e., 5.5 years after enrollment. This assumption is consistent with the advanced stage of disease observed in that patient population.

It should be stressed that the biases resulting from these extrapolations, if any, were likely to affect the two curves to the same extent and therefore would have exerted no substantial influence on our incremental analysis.

Cost-Effectiveness Ratio

In our primary cost-effectiveness analysis, the incremental cost-effectiveness ratio was calculated as $19,603 per undiscounted year of life gained. This value is the ratio of incremental costs ($901,723) to incremental benefits (46 undiscounted years of life gained), both normalized to 100 patients. In our secondary analysis (in which benefits were subjected to 5% discounting), the cost-effectiveness ratio was $20,494 per year of life gained. Incremental benefit in this analysis was 44 discounted years of life gained.

Sensitivity Analysis

In our first sensitivity analysis, a 20% increase in costs related to chemotherapy yielded a cost-effectiveness ratio of $22,793 per undiscounted year of life gained (or $23,829 per discounted year of life gained). The corresponding figure, with a 20% decrease in such costs, was $16,413 per undiscounted year of life gained (or $17,159 per discounted year of life gained). In our second sensitivity analysis, variations of ±20% in costs related to hospitalization, day hospital, and infection management yielded a cost-effectiveness ratio of $20,333 and $18,872, respectively, per undiscounted year of life gained. The corresponding figures of the cost per discounted year of life gained were $21,257 and $19,730, respectively. In our third sensitivity analysis (in which the two extrapolated tails of AUC were not included in the pharmacoeconomic calculations), the cost-effectiveness ratio was estimated as $15,960 per undiscounted life year gained (or $17,401 per discounted life year gained).

DISCUSSION

In recent years, cost-effectiveness analyses have increasingly been used to address controversial health care issues characterized by the need to define the role of high-cost medical interventions. Cost-effectiveness analyses are generally aimed at constructing a ratio with costs as the numerator and benefits (or effectiveness) as the denominator. While it is self-evident that monetary units are needed for quantifying costs, the problem of choosing appropriate units for measuring benefits, effectiveness, or outcome has long been debated. Health benefits, or effectiveness with regard to health, can in fact be expressed in a variety of ways, the most common being either disease specific units or years of life.[18–19]

The use of outcome measures that are specific to the particular disease examined corresponds to the most traditional form of cost-effectiveness analysis, denoted herein as first-generation cost-effectiveness analysis, in which typical clinical endpoints include, for example, relapses of Crohn's disease,[20] infections in premature babies[21] or in neutropenic adult patients,[22] complications of acute pancreatitis,[23] or adverse reactions to radiocontrast agents.[24–25] In examining these endpoints, first-generation cost-effectiveness analysis generally determines the "average" cost for avoiding one case with negative outcome (e.g., the cost of preventing an infection,[21–22] the cost of preventing an adverse reaction,[24–25] or the cost of preventing a disease recurrence[20]).

The use of more general outcome measures, namely, the number of life years gained, corresponds to techniques (denoted herein as second-generation or lifetime cost-effectiveness analysis) that allow for easier generalization of the results and therefore prove to be more useful for health care planning. An advantage of lifetime cost-effectiveness analysis is that its

primary endpoint is survival, a "hard" outcome measure (even though secondary endpoints can be handled as well, such as the frequency of infections evaluated in this study on paclitaxel). Another advantage is that lifetime evaluations can compare clinical problems among different therapeutic areas because their analyses are based on a more general outcome measure, the cost per year of life gained.

The application of lifetime cost-effectiveness analysis has recently been facilitated by the availability of least-squares curve-fitting methods based on Gompertz' law.[7-8,10] These methods utilize the experimental data of the first portion of a survival curve as a key element to predict the course of survival after the closing date of the clinical trial; in the framework of this approach, the gain in years of life is measured as the difference between the two areas under the survival curves.

In medical disciplines other than oncology, calculations of the cost per year of life gained have already focused on a variety of treatments, including, for example, antihypertensive therapy versus no treatment in hypertension ($20,000 per year of life gained[5-6]), hemodialysis versus no hemodialysis in renal failure ($35,000 per year of life gained[5-6]), tissue plasminogen activator versus streptokinase for myocardial infarction ($33,000 per year of life gained[5]), coronary bypass surgery versus medical therapy for left main coronary artery disease ($7000 per year of life gained[5-6]), interferon versus no treatment for chronic hepatitis B ($12,000 per year of life gained[9]), and long term therapy with beta-blockers after acute myocardial infarction ($3600–$23,000 per year of life gained[26]).

In the area of oncology, lifetime cost-effectiveness analyses have examined adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil versus no chemotherapy in lymph node–positive breast carcinoma ($1500 per year of life gained[7]), adjuvant systemic chemotherapy with fluorouracil and levamisole versus no adjuvant chemotherapy in colon carcinoma (about $2000 per year of life gained[27]), adjuvant intraportal chemotherapy versus no chemotherapy in colon carcinoma ($1200 per year of life gained[8]), and interferon versus cytotoxic agents as maintenance therapy for chronic myeloid leukemia (about $100,000 per year of life gained[19]).

One of the main goals of cost-effectiveness analysis (and particularly of lifetime studies) is to provide specific data for health care planners.[18] Alternative programs are ranked in terms of cost per year of life gained (from the lowest value to the highest) and selected from the top until available resources are exhausted. The point on the priority list at which the available resources are exhausted (or at which a particularly society is no longer willing to pay the price for the benefits achieved) becomes the society's cutoff level of permissible cost per unit of effectiveness. The upper limit for an acceptable cost-effectiveness ratio (expressed as dollars per year of life gained) remains controversial, but values in the range of $50,000 to $100,000 (or more) are generally considered too high.[5-6,18-19] In other words, interventions that imply a cost per year of life gained higher than the cutoff value of $50,000 are assigned an unfavorable cost-effectiveness ranking, whereas interventions characterized by a cost per year of life gained lower than this limit are considered acceptable.

A basic assumption of cost-effectiveness analysis is that one should always prefer a health care intervention that provides a population with more benefit per dollar than another intervention. However, as recently pointed out by Ubel et al.,[28] budget constraints can be a limiting factor that sometimes precludes the accessibility of the most cost-effective intervention to everyone in the population (thus raising issues of equity). One question that still needs resolution with regard to the interrelations between cost-effectiveness studies and budget constraints is which criteria are used to define budgets in the first place. The two main alternatives are the option of establishing a few "wide" budgets (with individual budgets covering a wide variety of different medical interventions) and the option of defining a large series of smaller budgets (with individual budgets being specifically oriented towards a single health care result). Consequently, the issue is on how many interventions are, on average, placed within a given budget, or, in other words, how many alternatives compete for the same budget (e.g., 2, 10, 100, or 1000 alternatives).

This problem of budget planning is a crucial question that is further complicated by the presence of marked organizational differences among different countries. On one hand, the overall health care budget available to a nation must be divided into a series of smaller secondary budgets; on the other hand, the aggregation criteria for establishing secondary budgets can depend on how many budgets are established, how often these values are revised, and how many competitors participate, on average, in the same budget. In the pharmaceutical area, for example, possible aggregation keys for budget definition include national budgets for outpatient drug reimbursement (where thousands of drugs compete with one another), hospital-based budgets for drug purchasing (where hundreds of drugs compete with one another), Diagnosis-Related Groups (DRGs) (where a few drugs compete with one another or with nonpharmacologic resources needed within a particular DRG), and budgets aimed at a very specific health care objective (e.g., a choice between two different screening programs for colon

carcinoma characterized by different costs and different efficacy).

When a fixed budget is allocated to a specific health care intervention (and this allocation of funds cannot, by definition, be revised), issues of equity emerge. Ubel et al.[28] have discussed a hypothetical example, a fixed budget of $200,000 to screen a population for colon carcinoma, characterized by the following restrictions: 1) the fixed budget was specifically allocated to that particular health care intervention; 2) two different programs were eligible for this particular health care intervention, and the first was clearly more cost-effective than the second; 3) there was a budget constraint that precluded a systematic application of the first program but permitted a systematic application of the second.

The most frequent reactions that Ubel et al. recorded in the context of this scenario were categorized as either 1) a viewpoint that recommended randomly providing the first program for the candidates of the population until the budget was exhausted (consequently, people who were not favored by this random selection eventually did not receive any form of medical intervention), or 2) another viewpoint that favored the systematic application of the second program to all candidates of the population. In addition, some of the people interviewed by Ubel et al. held the viewpoint that "offering a test to only [a subgroup of] the population is unfair, but at least it will show everyone that the system needs more money." While we substantially agree with this latter viewpoint, we believe that there is actually no satisfactory answer to the question raised by Ubel et al. unless one decides to revise the initial allocation of resources or in any event considers the possibility of increasing the budget at the expenses of other budgets for other types of health care intervention. Therefore, to use general terms, the problem is whether the ranking established by cost-effectiveness analysis must be restricted to the few competitors potentially suitable for a specific single-budget–health care result (without the possibility of modifying initial budgets), or whether this ranking must instead be extended to a large number of different competitors, including those belonging to other areas of medical intervention (in such a case, one does not generally preclude the possibility of revising budgets or reallocating funds).

While this question remains open, it is likely that widespread use of paclitaxel as a first-line treatment for advanced ovarian carcinoma will be thwarted by budget constraints. Hence, the various points discussed here earlier on the basis of the provocative article by Ubel et al. can apply to paclitaxel as well. In this context, the need to revise budgets specifically designed for the treatment of advanced ovarian carcinoma will probably emerge. Finally, it should be noted that while the application of budgets is generally very different among different countries, there is fortunately considerable international homogeneity among western countries in calculations of cost per year of life gained, such as those presented above. This finding suggests that scientific emphasis be placed on costs per year of life gained than on issues related to budget definitions.

Cost-effectiveness analysis is a very young scientific discipline. In this context, its basic needs still lie in a widespread application to provide data systematically on as many different issues of health care intervention as possible. In this way, priorities can be set not only within similar alternative programs with the same therapeutic goal, but also among different medical programs with completely different goals. This formidable challenge of ranking all health care priorities will involve future applications of cost-effectiveness analysis. However, at present it is premature to regard cost-effectiveness as a tool that will provide fully operative data on medical priorities.

In this framework of the continuing evolution of cost-effectiveness analysis, this study describes a typical application of a lifetime pharmacoeconomic evaluation based on the least-squares analysis of survival data. The therapeutic issue addressed in our study is particularly suitable for applying a lifetime technique, for the three following reasons:

1. A recent large-scale clinical trial is available in which the two treatment options of paclitaxel and cisplatin versus cyclophosphamide and cisplatin have been specifically compared.
2. In this trial, both survival curves were followed until a phase in which survival percentages declined to relatively low values (approximately 25–30% of residual survival at 4 years), and this specifically contributed to keeping the ratio between directly measured data versus extrapolated survival data within very favorable range (as documented by the relatively low percentages of tail AUCs reported previously).
3. The assumption that long term follow-up costs are similar between the two patient groups is realistic.

Our results show that despite the high cost of paclitaxel, the cost-effectiveness of the combination of paclitaxel and cisplatin as a first-line treatment for advanced ovarian carcinoma is favorable ($19,603 per undiscounted year of life gained, or $20,494 per discounted year of life gained). The lifetime approach adopted in our study (and the consequent measure of outcomes in terms of years of life gained) allows comparison of this result with data derived from the analysis of other forms of medical intervention.

Benchmarks against which the cost-effectiveness ratio of paclitaxel can be measured include the large series of oncologic and nononcologic examples presented previously. In this context, the value of about $20,000 per year of life gained found in our study shows the economic attractiveness of first-line chemotherapy with paclitaxel.

Our analysis was entirely based on the clinical results reported in the study by McGuire et al.[1] Because some criticisms have been raised with regard to the homogeneity of second-line treatments between the two patient groups in that study,[2-3] further data confirming the survival advantage found by McGuire et al. in the paclitaxel group will be needed.

One limitation of our study was that because of the lack of specific data, survival could not be measured in the context of the patients' quality of life,[29] and a cost-utility analysis could not therefore be performed. Regardless of this lack of quality-of-life data obtained within the study by McGuire's et al., the instruments currently available for measuring outcomes in terms of quality of life are not yet fully standardized,[29] and further methodological progress on this issue must be awaited.

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